per 1000 persons exposed to IG. This finding is in contrast to previous publications, which identified arterial events with higher rates than venous events.[4] This discrepancy may indicate that the high number of venous TEEs observed by Sridhar and colleagues may have been largely driven by cases of phlebitis or thrombophlebitis. Unfortunately, separate numbers for these types of events have not been provided by the authors. Pooling events such as myocardial infarction or deep vein thrombosis with events such as phlebitis and thrombophlebitis, which may be attributable to potentially different risk factors, does not allow for making a clear distinction between events associated with IGs themselves versus events that may be associated with the devices used for administering IGs. Estimates for peripheral venous catheter–associated thrombophlebitis rates range from 2% to 80%, and the risk of these events is correlated with the site and size of the catheter.[5]

It is important to recognize that claims-based data and data obtained through spontaneous reporting schemes (SRSs) cannot be directly compared. While claims-based data describe a finite data set, spontaneous data are subject to several limitations, with underreporting of an unknown extent and incomplete reporting representing two major limitations of SRSs. While the study of claims-based data has added an additional but important tool to evaluating product-related risks, it has obvious limitations such as lack of detail regarding individual events. Nonetheless, without research such as that published by Sridhar and colleagues the magnitude of the risk of IG-associated TEEs might still be underestimated, but discrepancies such as those we observed require substantial additional research to further understand the limitations of claims-based data to avoid premature assumptions, as well as premature regulatory decisions. Moreover, in our opinion the presented data for GGL and GGSD highlight the importance of SRSs and the necessity to carefully examine SRS data, clinical data, and data from new tools such as commercial databases and carefully weigh all available evidence, including the limitations of each of these data sources.

CONFLICT OF INTEREST

The authors report that they are or were employed by Baxter Healthcare and own stock in the company.

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Plasma exchange complications in patients treated for thrombotic thrombocytopenia purpura–hemolytic uremic syndrome: 2011 to 2014

Plasma exchange (PEX) is the standard treatment for patients with clinically suspected thrombotic thrombocytopenic purpura (TTP). Since the diagnosis of TTP may initially be uncertain, the decision to begin PEX in a patient with suspected TTP may be a difficult balance between the risk of severe TTP complications if treatment is delayed and the risk of severe PEX complications if treatment is begun. To document the frequency of PEX complications, the Oklahoma TTP-HUS Registry began in 1996 to prospectively document the outcomes of all PEX procedures for all consecutive patients in whom PEX was begun for an initial diagnosis of TTP, hemolytic uremic syndrome (HUS), or thrombotic microangiopathy (TMA).[1] We have subsequently reported each 3-year cohort of patients; our most recent report described data on all 302 consecutive patients, June 26, 1996, to June 25, 2011.[2] This report describes our subsequent experience with all 40

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TABLE 1. Major complications of PEX treatment in 12 patients, 2011 to 2014

Patient	Year	Hospital	Age, sex	PEX (No.)	AD13	CVC, Plasma	Description
1	2011	1	22, female	10	<5%	CVC	Cellulitis at left temporary IJ catheter insertion site, diagnosed 20 days after insertion, 6 days after discharge, 4 days after removing catheter, requiring hospitalization and systemic antibiotics.
2	2011	2	54, male	7	60%	Plasma	Hypotension, requiring treatment with norepinephrine.
3	2012	3	18, female	1	<5%	Plasma	Hypoxia, chest pain requiring stopping of PEX. No additional PEX was needed as the PLT count increased. Subsequently hereditary ADAMTS13 deficiency was confirmed by genetic testing.
4	2012	4	55, male	1	32%	CVC	Unsuccessful insertion of right temporary IJ catheter, hemorrhage requiring RBC transfusion.
5	2012	5	4, female	5	100%	CVC	Thrombosis of right femoral and iliac veins at catheter site, systemic anticoagulation.
6	2013	6	41, female	13	5%	Plasma	Hypocalcemia, arrhythmia requiring transfer to ICU.
7	2013	3	59, male	6	50%	CVC	Femoral catheter tip, *Staphylococcus epidermidis*, systemic antibiotics.
8	2013	6	78, male	23	6%	CVC	Blood culture, *S. epidermidis*, systemic antibiotics, temporary IJ catheter was removed.
9	2013	3	18, female	4	72%	CVC	Unsuccessful insertion femoral catheter, hemorrhage requiring RBC transfusion.
10	2013	1	47, female	7	100%	CVC	Blood culture and shoulder joint aspirate, MRSA, treated with systemic antibiotics.
11	2013	1	51, female	6	7%	CVC	Venous thrombosis at site of right IJ catheter, systemic anticoagulation.
12	2013	1	33, male	14	<5%	Plasma	Syncope and hypotension, required stopping of PEX.

AD13 = ADAMTS13 activity; CVC = central venous catheter–related complication; IJ = internal jugular vein; Plasma = plasma-related complication.

consecutive patients, June 26, 2011, to June 25, 2014, our sixth 3-year cohort of this study. Ten of the 40 patients had ADAMTS13 activity of less than 10%. The remaining 30 patients had alternative etiologies for their acute TMA episode. Patients were treated in nine different hospitals in the Oklahoma City region. Definitions of complications as major or minor and also as related to the central venous catheter or to plasma reactions have been previously described.[1]

Twelve (30%) of 40 patients had major complications; none died (Table 1). Eight patients had catheter-related complications (Patients 1, 4, 5, and 7-11). Four patients had plasma reactions that required stopping the PEX procedure (Patients 2, 3, 6, and 12). Analyses of these data demonstrated no significant association of major complications with the patient's hospital or with the year of occurrence. However, consistent with our previous cohorts,[2] the relative frequency of major complications was significantly greater among patients with ADAMTS13 activity of less than 10% (six of 10 patients, 60%) compared to patients with ADAMTS13 of at least 10% (six of 30 patients, 20%; p = 0.041). The greater frequency of major complications among patients with ADAMTS13 activity of less than 10% may be related to a greater number of days that PEX treatment was required: a median of 12 days (range, 1-34 days) compared to patients with ADAMTS13 of at least 10% (median, 7 days; range, 1-26 days, p = .0520). The types of major complications occurring in these 12 patients is similar to the types of major complications in the total 18-year experience of this study (Table 2). Seventeen (43%) patients had 25 minor complications, including seven patients who also had major complications. Minor complications included paresthesias, urticaria, and pruritis. Eighteen (45%) patients had no complications.

In our previous report, we described a significant trend across the five 3-year cohorts of this study toward fewer major complications which we attributed to a decreased duration of PEX treatment required to achieve remission, perhaps related to increased use of adjunctive treatments, corticosteroids, and rituximab.[2] Although the trend of decreasing frequency of major complications did not continue in the current cohort of patients, the frequency of major complications in this 3-year cohort (12 [30%] of 40) was not different from the frequency of major complications in the previous 3-year cohort (eight [15%] of 53, p = 0.083) or the previous 15 years of this study (72 [24%] of 302, p = 0.395).[2] Variation of the frequency of major PEX complication may be expected with our small numbers of patients who represent the experience of an entire community with many physicians in many different hospitals. Our total 18-year experience of a broad community practice emphasizes that major PEX complications remain common.

TABLE 2. Major complications of PEX treatment in patients with their initial episode of clinically diagnosed TTP, HUS, or TMA*

Complication	2011-2014 (n = 40)	1996-2014 (n = 342)
Catheter-related major complications		
Death	0	7
Pulmonary hemorrhage and pneumothorax	0	4
Systemic infection	0	3
Nonfatal complications	8	75
Systemic infection	3	37
Documented bacteremia	2	31
Suspected bacteremia†	1	4
Fungemia	0	2
Localized infection at catheter insertion site‡	1	3
Thrombosis	2	24
Catheter obstruction§	0	17
Venous thrombosis requiring systemic anticoagulation	2	7
Pulmonary hemorrhage	0	2
Retroperitoneal hemorrhage	0	1
Catheter insertion site hemorrhage‖	2	4
Pericardial tamponade	0	1
Pneumothorax¶	0	2
Insertion of incorrect catheter§	0	1
Plasma-related complications (no deaths have occurred)		
Hypotension requiring treatment	2	9
With syncope**	1	1
Anaphylaxis with cardiac arrest	0	1
Serum sickness	0	2
Hypoxia**	1	9
With chest pain	1	1
Vomiting**	0	1
Fluid overload††	0	1
Hypocalcemia, arrhythmia**	1	1

* The definition of major complications and the classification of complications as central venous catheter related or plasma related have been previously described.[1]
† Negative blood cultures but treatment with parenteral antibiotics for presumed sepsis.
‡ Required hospitalization and systemic antibiotics.
§ Required removal of the catheter and placement of a new catheter.
‖ Required RBC transfusion.
¶ Required placement of a chest tube.
** Required stopping PEX.
†† Required stopping PEX, intubation, and ventilation therapy.

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